REMARKS

I. Introduction

This amendment is in further response to the non-final Office Action dated April 9, 2007. An initial amendment was filed on August 9, 2007 which reordered and renumbered the claims of this application to make the prosecution history easier to follow. This amendment and the following remarks:

(1) set forth the substance of the July 31, 2007 interview at the Patent and Trademark Office with Examiners Betton and Royds and Supervisory Patent Examiner Marschel;

(2) amend applicants' claims to more particularly define the present invention; and

(3) present statistical information of the type considered in In re Wands regarding screening of compounds by Neurogen Corporation, the assignee of this application, for capsaicin receptor antagonists having the properties called for in amended independent Claim 223 (see the Declaration Under 37 CFR §1.132 of Alan J. Hutchison submitted herewith (the Hutchison Declaration)).

Attached hereto as Exhibits A-C are the following documents which were presented to the Examiners and discussed at the July 31st interview:

Exhibit A -- A list and the structures of capsaicin receptor antagonists that are not capsaicin analogues for which animal pain model data has been reported in the scientific literature.

Exhibit B -- A list and, where publicly available, the structures of capsaicin receptor antagonists which have been reported to have entered clinical trials.

Exhibit C -- A list of literature references which cite, employ as a reference compound, or employ as a test compound one of the capsaicin receptor antagonists disclosed in this application, i.e., compound

17 of applicant's Table III, now known in the industry as the "BCTC" compound. As noted in this exhibit, most of these articles are from pharmaceutical companies that compete with Neurogen and some of them acknowledge that the origin of the BCTC compound is the present application (more specifically, PCT Patent Publication No. WO 02/08221, which is the PCT counterpart and first publication of this application).

Also submitted herewith are copies of the literature references cited in these exhibits and a listing under 37 CFR §1.98(a)(1) of the references. The §1.98(a)(1) listing also includes the Bonache et al. article that was discussed at the interview (i.e., Bonache et al., "Old Molecules for New Receptors: Trp(Nps) Dipeptide Derivatives as Vanilloid TRPV1 Channel Blockers," ChemMedChem., 2006 Apr;1(4):429-38), as well as other references which applicants wish to make of record in this application. Copies of the references of the §1.98(a)(1) listing are submitted herewith.

II. The July 31st Interview and the Present Amendment

(A) The Bonache et al. Article

As discussed during the July 31st interview, the only issue remaining in this application is whether applicants' disclosure in combination with the level of ordinary skill in the art enable a skilled worker to practice the subject matter being claimed without the need for undue experimentation.

As presented to the Examiners at the interview, applicants believe that the recent (2006) article by Bonache et al. from the Instituto de Quimica Medica (Institute of Medical Chemistry) in Madrid, Spain, and associated institutions in Madrid, none of whose authors have any connection to Neurogen, provides a historical summary of work in this field which is relevant to the question of enablement. Specifically, this historical summary is relevant because it demonstrates that: (1) the methods for treating pain using the compounds called for by applicants' claims and (2) the procedures applicants disclosed for identifying those compounds have been successfully used in the art, i.e.,

those methods and procedures satisfy one of the clearest proofs of enablement -- they work in practice in the hands of others.[1]

In their article, Bonache et al. explain how capsaicin receptor antagonists (referred to by Bonache et al. as "TRPV1 antagonists") have been identified using conventional procedures well-known and widely used in the drug discovery field, including the in vitro receptor and in vivo analgesia assays that applicants describe for identifying and characterizing capsaicin receptor antagonists in their application.

After beginning with a summary of the use of capsaicin and other TRPV1 agonists as analgesics, Bonache et al. turn to the history of work on TRPV1 antagonists. They write:

> The TRPV1 antagonists reported to date...[include] capsaicin-competitive TRPV1 antagonists....Within [this] family, we find compounds related to vanilloid agonists, such as capsazepine and the 5-iodinated resiniferatoxin,[20,21] as well as diverse small molecules, structurally unrelated to vanilloids, which have emerged from high-throughput screening (HTS) programs. Potent TRPV1 antagonists, obtained after optimization of the initial HTS hits, mainly included di- and trisubstituted urea and thiourea derivatives,[22,23] N-aryl cinnamides,[25] and piperazine-1-benzimidazoles.[27] Some of these small molecules were highly active in animal models of chronic and inflammatory pain, including chronic pain states associated with bone cancer metastasis, and are currently under preclinical or clinical trials for a range of conditions.[26–27]

As can be seen from this passage, Bonache et al:

(a) distinguish between antagonists that are (i) "related to vanilloid agonists" and (ii) "diverse small molecules, structurally unrelated to vanilloids" (i.e., the antagonists that are the subject of applicants' claims; hereinafter referred to, when discussing Bonache et al., as the "diverse small molecules");

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[1] Submitted herewith are additional historical reviews of work in this field, specifically, review articles in which Neurogen scientists have been authors (see References 56, 57, 75, 93, and 100 of applicants' §1.98(a)(1) listing).

(b) explain how the diverse small molecules "have emerged from high-throughput screening (HTS) programs";

(c) further explain how various of the diverse small molecules have been found to be "highly active in animal models of chronic and inflammatory pain, including chronic pain states associated with bone cancer metastasis"; and

(d) as a result "are currently under preclinical or clinical trials for a range of conditions."

Accordingly, unlike the typical enablement case (e.g., In re Wright, 999 F2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993)), in this case, the subject matter of applicants' claims has been proven to work.

(B) High Throughput Screening (HTS) and Pain Models

With Bonache et al. as background, the July 31st interview next turned to a discussion of specific procedures which underpin the enablement of applicants' claims as of applicants' priority date.

As acknowledged by the Examiners during the interview, the use of high throughput screening (HTS) was conventional technology routinely used in the drug discovery process to identify compounds that act at a particular receptor. In this regard, three standard texts, all dated before applicants' July 20, 2000 earliest priority date, were brought to the interview and shown to the Examiners on this topic, i.e., High Throughput Screening: The Discovery of Bioactive Substances (1997), Combinatorial Chemistry and Technology: Principles, Methods, and Applications (1998), and Advances in Drug Discovery Techniques (1998). Submitted herewith are copies of the title pages and tables of contents of these texts.

As to the use of animal pain models to screen compounds identified by HTS, during the July 31st interview, the references of applicants' September 5, 2006 Response were again noted and the assertion in the April 9, 2007 Office Action that "[p]ain models generally have significant factors and susceptibilities that are of such a subjective nature that experimentation would be undue and burdensome" was

specifically addressed. It was pointed out to the Examiners that prior to applicants' earliest priority date, commercial equipment was being sold and used in the industry for conducting non-subjective pain model experiments, specifically, the Hargreaves thermal sensitivity test. The instruction manual for the commercial Hargreaves equipment used at Neurogen, i.e., the manual for Neurogen's "Ugo Basile Plantar Test (Hargreaves' Method)" device dated January 2000, was brought to the interview and shown to the Examiners. Submitted herewith is a copy of the front page and date page of this manual.

As noted during the July 31st interview, the Hargreaves thermal sensitivity test is one of the pain models referred to in applicants' specification. See paragraph [0392] of applicants' published application which cites Hargreaves original article in Pain (see Reference 46 of applicants' 9/5/06 Supplemental Modified 1449 Form).

Although not specifically mentioned at the interview, paragraphs [0410]-[0414] of applicants' published specification describe the use of the Hargreaves method to screen compounds for their ability to alleviate neuropathic pain. With regard to neuropathic pain, in the April 9th Office Action, the Examiner asserted that the present invention is unpredictable "due to the myriad of degrees of neuropathic pain, i.e., pain thresholds, which vary from individual to individual." As set forth on the front page of the Ugo Basile manual submitted herewith, one of the advantages of the Hargreaves method is that "[e]ach animal can serve as its own control." Thus, use of this screening method in connection with neuropathic pain, as applicants recommend in their specification, is one way recognized in the art for minimizing the effects of different pain thresholds for different individuals.

(C) The Proof Is in the Pudding

After discussing the Bonache et al. article and the Ugo Basile pain tester with the Examiners, the interview turned to real world evidence that the present invention works or, in the shorthand phrase used at the interview, that "the proof is in the pudding."[2]

[2]The complete phrase, which dates back to at least the 1600's (see Don Quixote), is: "the proof of the pudding is in the eating."

On this point, Exhibits A and B to this amendment were provided to the Examiners. Exhibit A is a list of capsaicin receptor antagonists for which animal pain model data has been reported in the scientific literature and Exhibit B is a list of the capsaicin receptor antagonists which have been reported to have entered clinical trials.

More particularly, Exhibit A shows (1) the chemical structures of the small molecule antagonists studied in these reports, all of which are not capsaicin analogues, (2) the methods by which the antagonists were discovered (e.g., by high throughput screening using a capsaicin-induced calcium flux assay; see Section II(E) below), and (3) the pain assessment models employed (e.g., thermal sensitivity). The exhibit also lists the affiliations of the investigators who performed the work, i.e., Abbott, Amgen, AmorePacific, GlaxoSmithKline, Johnson & Johnson, and Novartis.[3]

Exhibit B is a list and, where publicly available, the chemical structures of the compounds which have taken the next step and entered clinical trials. In this case, the companies are Amgen, GlaxoSmithKline, and Glenmark, as well as Neurogen in collaboration with Merck. Again, for all of the trials in Exhibit B for which structural information is available, the capsaicin receptor antagonists that have entered clinical trials are not capsaicin analogues.

(D) Neurogen's BCTC Compound

As additional evidence of the fact that their application is enabling, at the interview, the Examiners were provided with Exhibit C which is a list of literature references which cite, employ as a reference compound, or employ as a test compound a capsaicin receptor antagonist disclosed in this application, namely, compound 17 of applicant's Table III.

This compound is being commercially distributed by Biomol International, LP, and has become known in the industry as the "BCTC" compound. A copy of Biomol's catalogue entry and Material Safety Data Sheet for BCTC was provided to the Examiners during the interview and are submitted herewith (see Reference 51 of

[3] In Exhibit A, the reference to Drizin 2005 on the first page of the exhibit should be to Drizin 2006 (see Reference 63 of applicants' §1.98(a)(1) listing).

applicants' §1.98(a)(1) listing). As summarized by Amgen: "The BCTC template was disclosed for the first time by Neurogen and more recently by Johnson & Johnson, Bayer, GlaxoSmithKline, Abbott, and Purdue Pharma." (See Reference 81 of applicants' §1.98(a)(1) listing at page 1.)

As in most industries, it is rare for a pharmaceutical company to give credit to another pharmaceutical company for a technological advance, and even more rare for a company to give credit to a competitor's patent which disclosed the advance. Yet, as shown in Exhibit C and discussed with the Examiners, Purdue Pharma and Pfizer have both acknowledged that the capsaicin receptor antagonist they have studied (i.e., BCTC) is a compound of Neurogen's WO 02/08221, which is the PCT version of the present application. Likewise, Amgen has acknowledged that certain analogues of BCTC that it has worked on are based on Neurogen's disclosure of BCTC in WO 02/08221 (see Reference 81 of applicants' §1.98(a)(1) listing). A copy of WO 02/08221 is submitted herewith (see Reference 50 of applicants' §1.98(a)(1) listing).

(E) Claim Amendments and In re Wands

The last part of the July 31st interview dealt with claim amendments and In re Wands. At the interview, applicants proposed adding the following limitation to their claims: "wherein the capsaicin receptor antagonist competes with resiniferatoxin in a capsaicin receptor binding assay and exhibits a Ki value in such an assay that is less than 100 nM." This limitation is supported by, among other things, Example 10 of applicants' specification (see, in particular, paragraph [0331] for the 100 nM value) and for ease of reference, will be referred to hereinafter as the "Example 10 limitation."

As explained to the Examiners, one of the topics of the Bonache et al. article is an investigation into the mechanism of operation of certain di-peptides which had been shown in the 1980's to have analgesic effects. The Bonache et al. article hypothesizes that, at least in part, these di-peptides act at the capsaicin receptor. The article is, of course, not prior art to the present application since it was published in 2006, long after applicants' July 20, 2000 priority date. However, as discussed with the Examiners, to

avoid any question of inherent anticipation by the 1980's compounds, applicants proposed to incorporate the Example 10 limitation in their independent claim.

Along these same lines, the data of Jonassohn et al. and Smart et al. relating to isovelleral was also discussed with the Examiners (see References 72 and 89 of the §1.98(a)(1) listing submitted herewith; see also Jerman et al., Reference 6 of applicants' 10/17/05 Modified 1449 Form, for earlier data). Isovelleral is an antibiotic/antifeedant produced by the fungus *Lactarious vellereus* when injured and, as reported by Jonassohn et al., possesses potent mutagenic activity. Passing whether a skilled person would ever consider using a mutagenic compound as a medicine, as explained to the Examiners, the Example 10 limitation fully distinguishes isovelleral since as reported in the above references, its binding constant for the capsaicin receptor is substantially larger than 100 nM.

In connection with the discussion of the Example 10 limitation, the Examiners pointed out that one of the factual underpinnings of the CAFC's decision in In re Wands was the statistical information submitted by Wands et al. as to, in their case, the number of hybridoma clones that had been produced, the number tested, and the number that had achieved the binding constant specified in their claims. The Examiners suggested that corresponding information could be helpful in the present case.

In response, an investigation was performed regarding Neurogen's archival data relating to screening of its compound library for capsaicin receptor antagonists. That investigation revealed that the Example 10 analysis had been performed for certain compounds in the library, but the great majority of the screening had been performed using the calcium mobilization assay of Example 11 since it is preferable for high throughput screening.

Accordingly, applicants decided to move the Example 10 limitation discussed at the interview to dependent claims (i.e., Claims 224 and 229) and to switch to a limitation based on Example 11 for their independent claim (i.e., Claim 223) since that is the example for which Neurogen has the most screening data. In particular, as set forth above, applicants' independent Claim 223 has been amended to require that: "the

antagonist, when tested in a human capsaicin receptor calcium mobilization assay employing a calcium sensitive fluorescent dye, produces a decrease of at least 80% compared to a matched control in the fluorescence response generated by capsaicin when: (i) the antagonist concentration is 1 micromolar and (ii) the capsaicin concentration is equal to capsaicin's EC_{50} value for the assay" (hereinafter referred to for ease of reference as the "Example 11 limitation"). Support for the quantitative values of this limitation can be found in paragraph [0340] of applicants' published application.

Bonache et al. do not report calcium mobilization assay data for their di-peptides and thus in addition to the Example 11 limitation, independent Claim 223 has been amended to specify that the antagonist is "orally" administered. Support for this amendment can be found at, for example, paragraph [0234] of applicant's published application. As described on page 430 of the Bonache et al. article, in the 1980's, the Bonache di-peptides were administered by intracerebroventricular injection (i.c.v.), not orally.

As to isovelleral, both Jerman et al. and Smart et al. report the results of calcium mobilization experiments performed using a calcium sensitive fluorescent dye (see Figure 5B of Jerman et al. and Figure 5 of Smart et al.) and that data shows that isovelleral at a concentration of 1 micromolar does not achieve an 80% reduction in the measured fluorescence response. Accordingly, both the 1980's di-peptides discussed in Bonache et al. and isovelleral continue to be distinguished by the revised amendments to applicants' independent claim.

With regard to statistics, submitted herewith is a Rule 132 declaration by Dr. Alan Hutchison who, along with the undersigned and Dr. Seth Fidel, attended the July 31st interview. As set forth in his declaration, pursuant to the Examiners' recommendation, an analysis was performed of Neurogen's archival data relating to the screening of compounds in its library to identify capsaicin receptor antagonists. The analysis revealed that to date roughly 40% of Neurogen's library had been subjected to a human capsaicin receptor calcium mobilization assay at a compound concentration of 1 micromolar. In particular, 408,894 compounds, which had not been developed in

connection with Neurogen's capsaicin receptor antagonist project, had been tested in this way. Of those, the total number which achieved an 80% reduction in the fluorescence response was 3,467 of which 97 were capsaicin analogs, giving a final hit rate of 0.8%.

As set forth in paragraph 7 of Dr. Hutchison's declaration, when screening a compound library, a hit rate of greater than 0.1% is considered reasonable, a rate greater than 0.5% is very good, and a rate of 1% or more is considered excellent by workers in the art. The screening of Neurogen's library thus gave a hit rate between very good and excellent. As also discussed in paragraph 7 of his declaration, based on his experience at other pharmaceutical companies, Dr. Hutchison would expect that screening of other libraries would achieve at least a reasonable hit rate. And, of course, in this regard, the proof is again in the pudding as documented in: (1) the Bonache article's summary of how high throughput screening has been routinely and successfully used to find in Bonache et al.'s words "diverse small molecules, structurally unrelated to vanilloids" which function as capsaicin receptor antagonists; and (2) Exhibits A-C hereto.

III. Conclusion

In Wands, the CAFC wrote that "a determination [regarding undue experimentation] must be made in view of the circumstances of each case and cannot be made solely by reference to a particular numerical cutoff." 8 USPQ2d at 1406 n.29.

Applicants respectfully submit that when the circumstances of this case, as set forth above, are considered it is evident that a person of ordinary skill in the art can practice the present invention without undue experimentation. Accordingly, applicants believe that the §112, ¶1, rejection should be withdrawn and that this application should be allowed. Such action is respectfully requested.

Respectfully submitted,

Date: 10/9/07

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Capsaicin Receptor Antagonists That Are Not Capsaicin Analogues For Which Animal Pain Model Data Has Been Reported In The Scientific Literature*

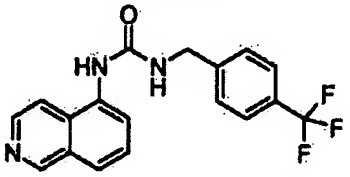
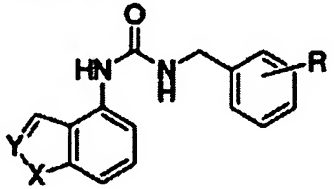
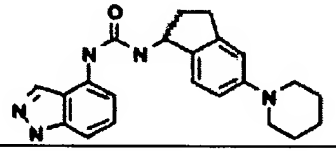
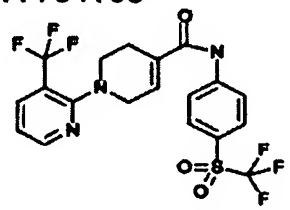
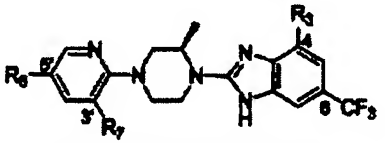
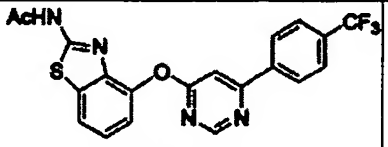
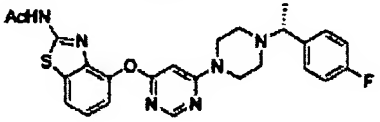
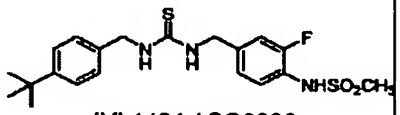
Company	Compound	How Discovered	Pain Assessment	Reference(s)
Abbott	A-425619 	HTS & Optimization	CFA-induced thermal, Carageenan-induced thermal, Skin incision -induced thermal & mechanical, Hotplate, Formalin, Nerve ligation, Nerve constriction Capsaicin induced mechanical, & osteoarthritic model	El Kouhen 2005 Honore 2005
Abbott	 X=NH Y=N R=3,4-DiCl	Optimization of A-425619	CFA-induced thermal Nerve ligation Writhing	Drizin 2005
Abbott	A-795614 	"capsaicin-induced calcium flux assay using a fluorometric imaging plate reader"	CFA-induced thermal, CFA-induced mechanical, Capsaicin induced mechanical, & osteoarthritic model	Cui 2006
Abbott	A-784168 	"capsaicin-induced calcium flux assay using a fluorometric imaging plate reader"	CFA-induced thermal, CFA-induced mechanical, Capsaicin induced mechanical, & osteoarthritic model	Cui 2006

Exhibit A

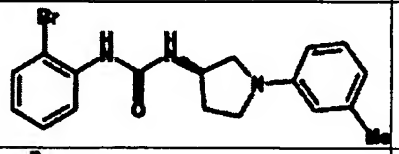
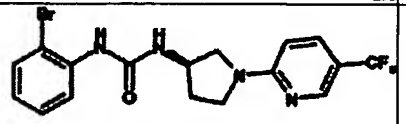
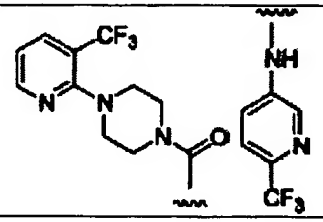
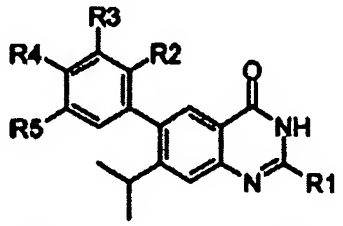
*All act at the capsaicin receptor with K_i values of less than 100 nM.

Capsaicin Receptor Antagonists That Are Not Capsaicin Analogues For Which Animal Pain Model Data Has Been Reported In The Scientific Literature*

Company	Compound	How Discovered	Pain Assessment	Reference(s)
Amgen	 R3=4-(3,4,5-trifluoro-Ph) R6=(*R,S*)-CH(OH)CH_2OH R7=Cl	"Based on conformationally constrained analogues of BCTC"	CFA-induced thermal & Capsaicin-induced flinch	Ognyanov 2006
Amgen	 AMG 517	HTS & Optimization	CFA-induced thermal & Capsaicin-induced flinch model	Doherty 2007
Amgen	 AMG 628	Optimization of AMG 517	CFA-induced thermal & Capsaicin-induced flinch model	Wang 2007
AmorePacific	 JYL1421 / SC0030	Derivatization of ultra-potent agonists	Writhing	Suh 2003

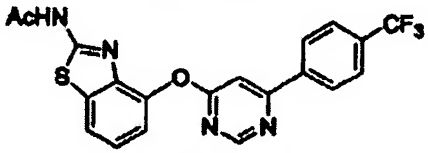
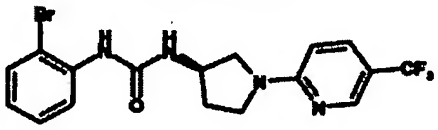
*All act at the capsaicin receptor with K_i values of less than 100 nM.

Capsaicin Receptor Antagonists That Are Not Capsaicin Analogues For Which Animal Pain Model Data Has Been Reported In The Scientific Literature*

Company	Compound	How Discovered	Pain Assessment	Reference(s)
GlaxoSmithKline		HTS & Optimization	Capsaicin induced mechanical	Rami 2006
GlaxoSmithKline	 SB-705498	HTS & Optimization	Capsaicin induced mechanical & CFA-induced	Rami 2006 Gunthorpe 2007
Johnson & Johnson		HTS & Optimization	Capsaicin-induced mechanical & NADA-induced thermal	Swanson 2005
Novartis	 R1=Me, R2=H, R3=$OCH_2{}^cPr$ R4=Cl, R5=H	HTS & Optimization	Capsaicin induced mechanical & Nerve ligation	Culshaw 2006

*All act at the capsaicin receptor with K_i values of less than 100 nM.

Capsaicin Receptor Antagonists Reported To Be Entered Into Clinical Trials*

Company	Compound	Phase
Amgen	AMG 517 	I
GlaxoSmith-Kline	SB-705498 	II
Neurogen & Merck	NGD 8243 / MK-2295 not capsaicin analog	II
Glenmark	GRC 6211	II

*All act at the capsaicin receptor with K_i values of less than 100 nM.

Exhibit B

Neurogen's BCTC Compound

Company	BCTC	Reference
Abbott	Cited	Cui 2006
Amgen	Used as a Reference Compound	Gavva 2005a
Amgen	Used as a Reference Compound	Gavva 2005b
Amgen	Analogues Used as Test Compound; Neurogen's WO 02/08221 Cited	Ognyanov 2006
Astellas Pharma	Used as a Test Compound	Saitoh 2007
GlaxoSmithKline	Used as a Reference Compound	Weil 2005
GlaxoSmithKline	Cited	Gunthorpe 2007
Grunenthal	BCTC Derivative and BCTC Used as Test Compounds	Behrendt 2004
Grunenthal	Derivative Used as a Test Compound	Christoph 2007
Johnson & Johnson	Cited	Jetter 2004
Johnson & Johnson	Neurogen's WO 02/08221 Cited	Swanson 2005
Johnson & Johnson	Used as a Test Compound	Liu 2006
Katholieke Universiteit Leuven University of Hawaii	Used as a Test Compound	Cuypers 2006
Pfizer	Used as a Test Compound	Kanai * 2005
Pfizer	Used as a Test Compound	Kanai * 2007
Purdue Pharma	Used as a Test Compound	Pomonis * 2002
Purdue Pharma	Used as a Test Compound	Valenzano * 2003
Purdue Pharma	Used as a Test Compound	Pomonis 2003

* Neurogen's WO 02/08221 specifically acknowleded as basis for the use of BCTC.

Exhibit C

Purdue Pharma	Neurogen's WO 02/08221 Cited	Sun 2003
Purdue Pharma	Used as Lead Compound	Tafesse 2004
Purdue Pharma	Used as Lead Compound	Shao 2005
Schering-Plough	Used as a Test Compound	Phelps 2005
Schering-Plough	Used as a Test Compound	McLeod 2006
Seoul National University National Cancer Institute	Cited	Lee 2004a
Seoul National University National Cancer Institute	Cited	Lee 2004b
University of Pécs	Cited	Jakab 2005
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